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# Chronic pulmonary aspergillosis in two malnourished patients

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## Abstract

Invasive aspergillosis typically occurs in patients with severe immune function deficiencies such as haematopoietic stem cell or solid organ transplant recipient. Chronic pulmonary aspergillosis (CPA) occurs mainly in patients with some degree of immunosuppression (i.e. AIDS, diabetes, long term corticosteroid) but may affect also patients without classical signs of immunosuppression, in which diagnosis is challenging. Here two cases of CPA associated with malnutrition as predisposing factor are reported.

## Keywords

chronic pulmonary aspergillosis; malnutrition; immunosuppression; voriconazole

## Abbreviations

CPA: chronic pulmonary aspergillosis; AIDS: acquired immunodeficiency syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ESBL: extended spectrum beta lactamase; CRP: C reactive protein; LH: Luteinizing hormone; IGF1: insulin growth factor 1; GH: growth hormone

## Introduction

Invasive aspergillosis typically occurs in patients with severe immune function deficiencies such as haematopoietic stem cell or solid organ transplant recipients [1]. Chronic pulmonary aspergillosis (CPA) occurs in patients with some degree of immunosuppression (i.e. AIDS, diabetes, long term corticosteroid) and it is less angioinvasive and with a relatively slow and indolent progression [2]. CPA may affect also patients without classical signs of immunosuppression, in which diagnosis is challenging. Here two cases of CPA associated with malnutrition as predisposing factor are reported, whose management was complicated for clinicians due to delayed diagnosis and challenging clinical course. To our knowledge these are the first case reports in which malnutrition was the predisposing factor for aspergillosis.

## Case Series

**n1:** A 82 years old female patient was admitted on Internal Medicine Ward on the 24$^{th}$ September 2016 due to confusion and hypercalcemia (serum calcium 12.3 mg/dl) and malnutrition (BMI 15). She had a history of dementia and epilepsy treated with carbamazepine. At the admission prealbumin value was 10 mg/dl and transferrin value 78 ng/ml. She received a short term therapy with steroids associated

with clodronate for hypercalcemia. The chest X-ray performed on admission was negative for pleuro-polmunary lesions (Fig 1). *E coli* ESBL was isolated from urine culture and was treated with meropenem. The count of lymphocites was 1823 cell/ul (nv 690 – 2540 cell/ul), CD4+ 922 cell/ul (nv 410 – 1590 cell/ul), CD8+ 913cell/ul (nv 190 – 1140 cell/ul), CD4/CD8 1.0 (nv 1,14 - 2,50).

On 5th October the patients was symptomatic for cough and lung secretions and CRP increase. A new chest X-ray showed an excavate nodular lesion in right medium lobe (Fig 2). The next day a chest CT scan with contrast medium confirmed the presence of a 4.5 cm nodular lesion in upper right lobe with ground glass and without contrast enhancement (Fig 3). *Candida glabrata* grew on bronchoalveolar lavage culture (10/10/16); then, on the 17th October sputum culture grew positive for *Aspergillus fumigatus.* Galactomannan on BAL was not tested, serum galactomannan tested negative twice. Oral voriconazole was started on 20th October (300 mg every 12 ore three times, then 150 mg every 12 ore), without clinical improvement. Considering the potential interaction with carbamazepine, a pharmacokinetics evaluation was performed. Voriconazole tested undetectable (range 1-4 microg/mL-homogenous enzyme immunoassay) while carbamazepine plasma level was 10.70 mg/L (range 4 e 12 mg/L; particle enhanced turbidimetric inhibition immunoassay method). On 27th October voriconazole daily dose was increased (250 mg every 12 ours) but it still remained undetectable on plasma. After few days an increase in liver function tests was observed (GGT 803 mU/ml, ALT 133 mU/ml and AST 119 mU/ml ) was attributed to voriconazole, thus voriconazole was stopped and liposomal amphotericin B started (3 mg/Kd daily). The general condition of the patient did not improve. On 6th November she died due to a septic shock (*Proteus mirabilis* ESBL from urine culture was isolated post mortem).

**n2:** A 36 year old men was admitted to a Neurology Department on 19th November 2012 because of an important weight loss (around 22 Kg) in the last 2 years, apparently associated with financial and personal problems. He was a previous smoker. On admission he complained of fever and cough, he was cachectic (body weight 32 Kg, BMI 12.3 Kg/m$^2$) and his blood pressure was 80/40 mmHg. Prealbumin blood level was 11 mg/dl (n.v. 20-40 mg/dl). He tested HIV negative; thyroid function was normal; celiac disease antibodies were negative. The suspect of anorexia nervosa was confirmed by his hormonal profile (IGF-1 below detection limit, GH increased, testosterone decreased and LH within normal range).

Treatment with citalopram and bromazepam was started. The total number of lymphocytes were 864/ul, CD4+ 463/ul, CD8 117/ul, CD4/CD8 3.9. On 21st November a chest CT scan showed excavated lesions (32x22 mm) on the right upper lobe of the lung (Fig 4), suggestive for tuberculosis. The patient underwent a bronchoscopy with bronchoalveolar lavage. Bronchoalveolar-lavage culture was positive for *Aspergillus terreus* and *g*alactomannan antigen too (value 6.12 n.v. < 0.5) (galactomannan was negative in serum). The patient was then transferred to an Infectious Disease Clinic. He was treated with voriconazole iv, because of poor compliance of the patients with oral treatment. On 30th November a new chest CT scan was performed and it ruled out blood vessels involvement. Considering the poor general condition of the patient the thoracic surgeon excluded the possibility of a surgical intervention. A CT scan showed reduced pulmonary lesions after four weeks of voriconazole (Fig 5). The patient was discharged with gastroenteric feeding tube (voriconazole tablets were grinded and administered through the feeding tube). Patient's general conditions and his nutritional state improved in the following months. Voriconazole treatment lasted 3 months. A new chest CT scan was performed in march 2013 (Fig 6).

Cavitary lesions appeared to be slightly increased, while a PET-CT excluded the presence of active infections, therefore the patients was not retreated. On the 23rd of August 2013 a CT images showed favorable evolution with presence of fibrosis (Fig 6).

## Discussion

CPA designates a form of Aspergillosis that occurs frequently in patients with different respiratory pathologies (i.e. tuberculosis, sarcoidosis, COPD) [1]. Other conditions of immune deficiency can be associated with an increased CPA risk such as cirrhosis, diabetes and HIV infection [2]. CPA diagnosis can be difficult, particularly if neither a history of immune depression nor typical concomitant diseases are reported. In both cases here described, malnutrition was the mainly predisposing factor. Malnutrition-induced immune suppression is a major cause of morbidity and mortality in multiple susceptible patient populations. Apparently T dependent immune function was substantially normal in both patients, as evidenced the absolute CD4 and CD8+ cells count value in the normal range. Nevertheless malnourished patients may have altered T lymphocytes function, in particular malnutrition shifts the balance of pro-inflammatory Th1 versus anti-inflammatory Th2 cytokines and may therefore predispose to infection [3]. For example, malnutrition represents an independent risk factor for aspergillosis or other forms of zygomycosis in patients with hematological malignancy [4].

Diagnosis of CPA is often challenging, in particular in patients without classical risk factors for invasive fungal diseases and requires the combination of characteristics including radiological pattern (typically a new cavitary lesion), direct evidence of Aspergillus infection by culture (sputum and/or BAL) or an immunological response to Aspergillus [5]. BAL galactomannan is a reliable diagnostic marker with high sensitivity and specificity that should be routinely evaluated in the suspect of CPA, while serum galattomanan is typically negative [6]. In the first patient galactomannan on BAL was not performed and diagnosis was possible only on a repeated sputum culture, performed because of suspicious radiologic lesion. It is therefore suggested to request routinely both BAL cultures and galactomannan when suspicious lesions are observed otherwise diagnosis can be delayed.

Voriconazole is the treatment of choice of CPA, it is formulated as tablets or as a sulfobutyl-ether cyclodextrin solution for IV administration. The oral formulation has good bioavailability in the fed or fasted state and is preferred when it is possible. Voriconazole is effective [7] but has a narrow therapeutic range and displays multiple drug-drug interactions therefore requires expertise management. For all these reasons concomitant treatments should be carefully evaluated and periodic pharmacokinetic monitoring is advocated [8,9]. In the first patient here reported voriconazole was not effective due to an interaction with carbamazepine that led to significant reduction of voriconazole plasma levels. The duration of treatment is usually 4-6 months and it could be longer if the patient shows a slow response [2]. In the second case treatment with voriconazole was shorter than suggested by guidelines as the improvement of nutritional state was associated with disappearing of respiratory symptoms and radiological lesion.

In conclusion, patients with CPA can be admitted to internal medicine wards and diagnosis can be difficult for not expert clinicians, also management requires expertise due to possible drug-drug interactions and side effects.

## Figures

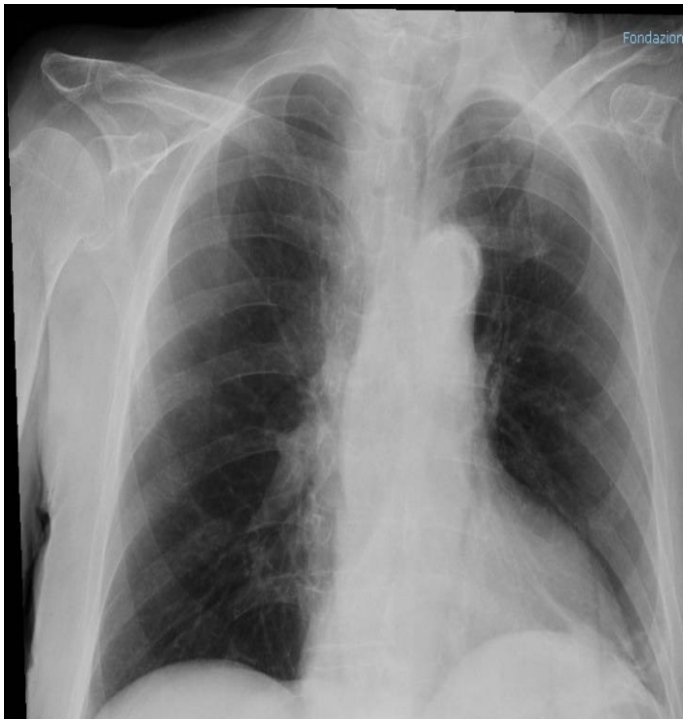

**Figure 1:** Normal Chest X-ray on admission (patient 1)

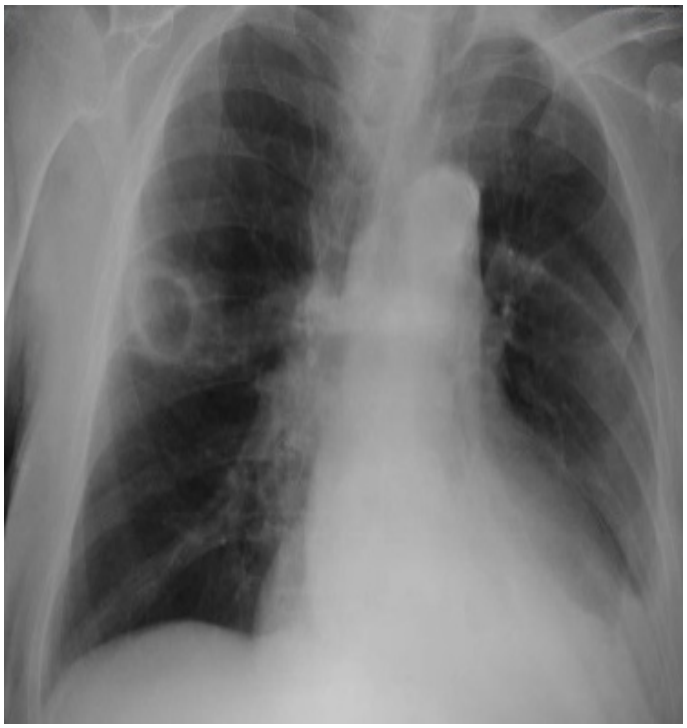

**Figure 2:** Excavate nodular lesion in right medium lobe (patient 1)

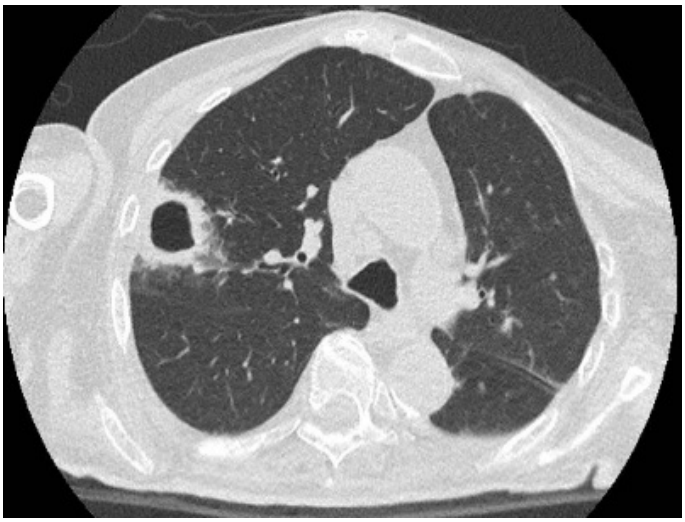

**Figure 3:** Nodular lesion of 4.5 cm in upper right lobe with ground glass (patient 1)

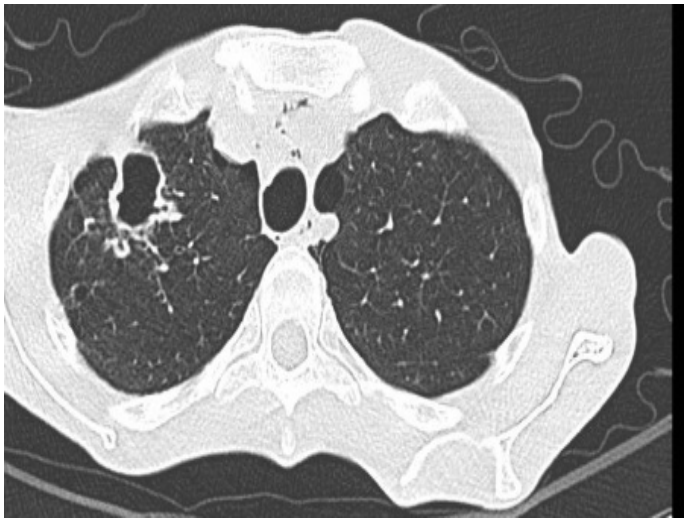

**Figure 4:** Excavated lesion of 32x22 mm on the right upper lobe (patient 2)

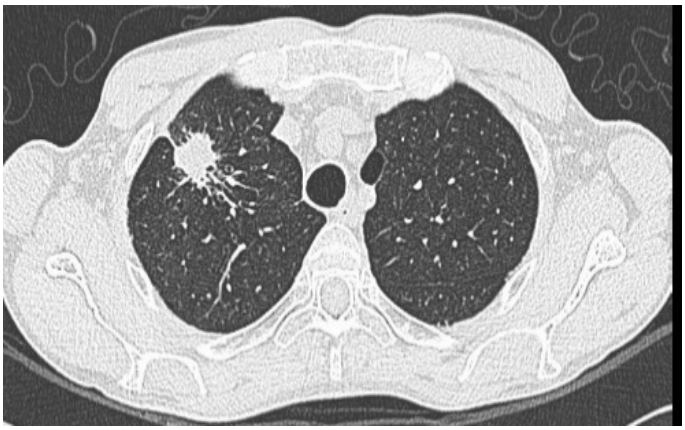

**Figure 5:** Light increase in dimension of excavated lesions after 3 month of therapy (patient 2)

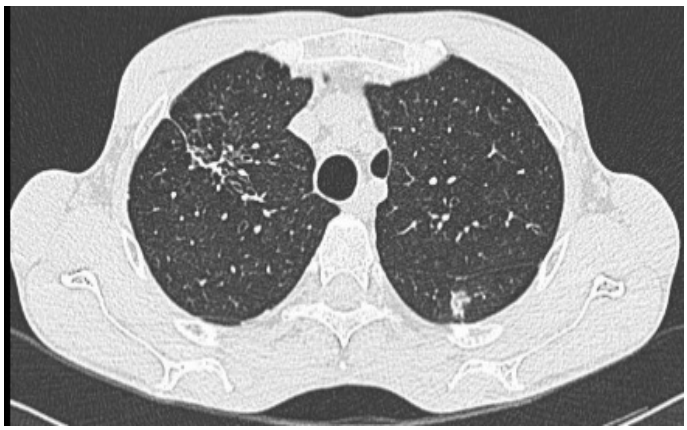

**Figure 6:** Fibrotic evolution of the lesions (patient 2)

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